

Helix-coil Transition in Closed Circular DNA

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ABSTRACT A simplified model for the closed circular DNA (ccDNA) is proposed to describe some specific features of the helix-coil transition in such molecule. The Hamiltonian of ccDNA is related to the one introduced earlier for the linear DNA. The basic assumption is that the reduced energy of the hydrogen bond is not constant through the transition process but depends effectively on the fraction of already broken bonds. A transformation formula is obtained which relates the temperature of ccDNA at a given degree of helicity during the transition to the temperature of the corresponding linear chain at the same degree of helicity. The formula provides a simple method to calculate the melting curve for the ccDNA from the experimental melting curve of the linear DNA with the same nucleotide sequence.

INTRODUCTION

In its biological “native” state, a DNA molecule has a form of well-known right-handed double helix (Crick and Watson, 1954), wherein two heteropolymer chains are wound around each other. The double helical structure is believed to be the structure of minimum free energy, under the normal physiological conditions. It is stabilized by many factors, among which the most essentials are hydrogen bonds between complementary nitrogenous bases (A-T and G-C) on opposite chains and the interactions between neighboring base pairs along the chain (stacking of base pairs), which have a hydrophobic nature. When the environmental conditions are changed, two chains can separate from each other along some parts of the molecule, giving rise to the loops, bordered by helical regions. The double helix can also unwind completely and split into two separate chains. Thus the whole molecule or its parts undergo the transition from the state of energetically favorable high-ordered helical structure into the state of disordered coil with large entropy. This process is known

as helix-coil transition. Alternative names are “melting” or “denaturation”. The helix-coil transition can be caused by many factors. In the living cell it is mediated by specific protein molecules, in *in vitro* experiments it may be realized by changing the temperature, chemical composition, the concentration of salts, etc. of the DNA solution.

The helix-coil transition in DNA has been a subject of very intensive theoretical investigations since 1960s (Poland and Scheraga, 1970; Flory, 1969; Volkenshtein, 1977; Vedenov et al., 1972; Wartell and Benight, 1985; Wada and Suyama., 1986; Grosberg and Khokhlov, 1994); for the foundations of theory, see e.g. (Poland and Scheraga, 1970; Flory, 1969; Volkenshtein, 1977) ; for reviews of earlier research works, see e.g. (Vedenov et al., 1972; Wartell and Benight, 1985; Wada and Suyama., 1986); for review of more recent developments, see e.g. (Grosberg and Khokhlov, 1994) Here we make just several very short remarks on the background of the helix-coil transition.

The most interesting feature of the helix-coil transition in DNA is its cooperativity which is a manifestation of long-range interactions along the chain. Many factors can influence the degree of the cooperativity. It depends, for example, on the base sequence of DNA, on the chain length, ionic strength of the solution, etc.

The usual way for describing the helix-coil transition is to find the dependence of the *degree of helicity*, θ , on the external parameter (e.g. the temperature); θ is defined as the average fraction of the bounded pairs: $\theta = \langle n \rangle / N$, where N is the total number of base pairs and $\langle n \rangle$ is the average number of the bounded pairs. The graph of this dependence is called a “melting curve”. The temperature at which $\theta = 1/2$ is called melting point (T_m) and is one of the characteristics of the melting process. Another quantitative characteristic is the “melting interval” or the width of melting $\Delta T = [\frac{\partial \theta}{\partial T}]^{-1}$, where the derivative is taken at the point T_m . ΔT is an actual measure of the cooperativity. The smaller is the melting interval the more cooperative is the transition.

Traditionally the theoretical models for helix-coil transition are based on the assumption that every base pair can be in two possible states: hydrogen-bonded (helix) or open (coil). This makes it convenient to use the Ising model for ferromagnets as a basic tool to describe the helix-coil transition. Usually four parameters are introduced into models: (1) The helix stability parameter s , called also the equilibrium constant of helix growth. It corresponds to the statistical weight of the helical base pair, which follows a helical one. (2) The cooperativity parameter σ (or helix initialization constant), which corresponds to the statistical

weight of a bonded pair at the junction of the helical and coil regions of the chain. The actual values of these two parameters are averaged over all conformations of the molecule or over the ensemble of identical molecules. (3) The loop-weighting factor $m^{-\alpha}$, where m is the number of bases in the loop, and $\alpha = 1.5 - 1.7$ is called *Jackobson-Stockmayer exponent* (Jacobson and Stockmayer, 1950). The meaning of this factor is that the entropy of the melted loop of m base pairs is different from the entropy of m open pairs at the free ends of the molecule. In other words, the entropy is not additive inside the loop (Poland and Scheraga, 1966) (4) Another factor, which affects the nature of helix-coil transition is called *dissociation equilibrium constant*. It corresponds to the process, when the last bond opens, and the molecule splits into two fully separated strands. Note that the classical Ising model does not contain last two factors and must be modified correspondingly.

An even more topologically complex object is the closed circular DNA molecule, which typically occurs in some simple biological systems (plasmids, viruses) and in cytoplasm of the animal cells (Dulbecco and Vogt, 1963; Weil and Vinograd, 1963). In this form the double-helical DNA is twisted in such a way that the first monomer of the sugar-phosphate backbone of each chain is covalently linked to the last one to make up a closed circle (Fig. 1). The topologically similar structures may occur also in the cells of higher animals in which some DNA molecules are wound around the specific protein structures (histones). Double helical closed circular DNA (ccDNA) typically exists in the conformation of so called supercoil which represents a sort of interwound structure. The degree of supercoiling as well as the topological state of supercoil are described by a linking number (Vologodskii, 1992). Many papers on experimental and theoretical investigations of ccDNA have been published (Marko and Siggia, 1995 and references therein). One of the interesting problems is the helix-coil transition in these molecules. Because of the specific topological restraints some features of the helix-coil transition in ccDNA differ from those of linear DNA. For example, experiments show that the melting process of a ccDNA begins at a lower temperature than that in a linear DNA, and completes at considerably higher temperatures (Vinograd et al., 1968). In (Laiken, 1973; Anshelevich et al., 1979; Vologodskii et al., 1979; Benham, 1979; Benham, 1980; Vologodskii and Frank-Kamenetskii, 1981; Belintsev, B. N. and A.V. Gagua. 1989) a mean field theory for melting of the ccDNA is developed. The general assumption in these works is that the total energy of ccDNA consists of two parts: the term corresponding to the ordinary DNA, and the term corresponding to the fact that the molecule under description

is a closed circular system (superhelix term).

In (Hayryan et al., 1990; Hayryan et al., 1995) some of us have developed a microscopical theory of helix-coil transition in polypeptide chains which doesn't include averaged phenomenological parameters like s and σ and is based on the molecular characteristics of the chain. A many-particle Potts-like model was used instead of the two-state Ising model. Since the model was able to reproduce qualitatively many important characteristics of the helix-coil transition in polypeptides, we were encouraged to use a similar approach to the linear DNA molecule. It appeared that the secular equation of the DNA Hamiltonian may be written in exactly the same form as for polypeptide chain in which the characteristic length of hydrogen bond is replaced by some characteristic length of DNA molecule. The model was published in (Morozov et al., 2000) and will be reviewed briefly in Sec. II of the present paper.

The purpose of the present work is to continue the microscopical approach by applying it to the melting process of ccDNA, using an Hamiltonian approach, similar to one which was used for polypeptides and linear DNA. We are going to show that the model of ccDNA can be reduced to the model of linear DNA (which was in its turn reduced to the polypeptide model with appropriate redefinition of parameters). We do not consider explicitly the topological restraints, nor the superhelic structure of ccDNA. Instead we impose some specific conditions on the mechanism of breaking of the hydrogen bonds. We obtain a transformation formula which relates the temperature of ccDNA for a given degree of helicity to the temperature of the linear DNA for the same degree of helicity. Using this transformation formula, we suggest a simple method to obtain the melting curves for the ccDNA from the melting curves of the corresponding linear DNA.

This paper is organized as follows: In Sec. II we briefly review the model of linear DNA. In Sec. III we introduce the model of ccDNA. In Sec. IV the melting curve for ccDNA is related to melting curve for linear DNA. Some problems for further studies are discussed in Sec. V.

THE MODEL OF THE LINEAR DNA

Consider a double-chain DNA molecule which consists of solely one kind of complementary nitrogen base pairs, either A-T or G-C, which are displaced randomly along the chain.

Let the monomers in each chain be enumerated $0, 1, 2, \dots, N$. In this case one can assume that the inter-chain hydrogen bonds are formed only between the bases with the same order number because the probability of mismatching of the bases is extremely small due to the randomness of the sequence.

We construct the model of such a system as follows (Morozov et al., 2000). To each repeated unit i of one chain of the double helix a vector \vec{a}_i is assigned. Similarly, the vector \vec{b}_i is assigned to the i -th unit of the opposite chain. One can consider these vectors as directed along the line connecting two adjacent sugar rings. We also assign a vector \vec{d}_i to each complementary pair of nitrogen bases. The magnitude of this vector is not important. We will just assume that all \vec{d}_i emanate always from the same chain. When the corresponding complementary pair is in the helical conformation, the vector \vec{d}_i connects the ends of vectors \vec{a}_i and \vec{b}_i . For the sake of simplicity, we assume that the first (number 0) complementary pair is always in the helical conformation and the bases are connected by the vector \vec{d}_0 . Figure 2 shows the scheme of hydrogen bond formation.

When the i -th complementary pair is also in the helical conformation then we assume that the loop $0 - (i - 1)$ is formed. Geometrically this means that

$$-\vec{d}_0 + \sum_{k=1}^i \vec{a}_k + \vec{d}_i - \sum_{k=1}^i \vec{b}_k = 0, \quad (1)$$

Let $\vec{\gamma}_k = -\vec{d}_{k-1} + \vec{a}_k - \vec{b}_k + \vec{d}_k$, then Eq. (1) may be rewritten as

$$\sum_{k=1}^i \vec{\gamma}_k = 0. \quad (2)$$

Note that if the hydrogen bond in the i -th pair is formed then (2) holds true even if there are no other hydrogen bonds in any of the pairs between the first and the i -th pairs.

The Hamiltonian of the chain then reads

$$-\beta H = J \sum_{i=1}^N \delta \left(\sum_{k=1}^i \vec{\gamma}_k, 0 \right), \quad (3)$$

where $J = U/T$, $\beta = T^{-1}$ and δ is the Kronecker delta symbol with U being the energy for hydrogen bond formation in one complementary pair. To be more precise, the quantity U is the energy of the helical state of one base pair, i.e., it includes also the stacking of bases (Morozov et al., 2000). Here an approximation is done that the stacking interactions are

the same for all base pairs throughout the chain. Further in the text we will use for (3) the form

$$-\beta H = J \sum_{i=1}^N \delta_1^{(i)}, \quad (4)$$

where the notation $\delta_1^{(i)} = \delta \left(\sum_{k=1}^i \vec{\gamma}_k, 0 \right)$ is introduced.

We should mention an important feature of the Hamiltonian (3). Though the first sum is extended over the number of base pairs, it doesn't mean that the contributions from different base pairs are independent. The term in the brackets shows that the state of i th pair, hence its contribution, depends on the states of all previous $(i - 1)$ pairs. Thus, the cooperative interdependence of successive linked base pairs is implicitly included through real geometrical restrictions.

For infinitely long chain one has the following equations for the partition function and the free energy, respectively:

$$Z = P_0^{-N}, \quad (5)$$

$$F = T \ln P_0, \quad (6)$$

where P_0 is the nearest to zero root of the secular equation for Hamiltonian (4) (Hayryan et al., 1990; Morozov et al., 2000)

$$\sum_{m=1}^{\infty} P^m \varphi(m) = \frac{1}{V}, \quad (7)$$

where $V = e^J - 1$ and

$$\varphi(m) = Q^{-m} \sum_{\gamma_1} \sum_{\gamma_2} \dots \sum_{\gamma_m} \delta_i^{(m)}. \quad (8)$$

Here Q is the number of conformations of the repeated unit and bears the same meaning as in the case of polypeptide chain (Hayryan et al., 1990; Hayryan et al., 1995). Namely,

$$Q = \frac{\text{Partition function of one repeated unit}}{\text{Partition function of one repeated unit in helical structure}}. \quad (9)$$

The meaning of the function $\varphi(m)$ may be interpreted as the ratio of the partition function of the loop of m units to that of the same chain without loops.

The secular equation (7) contains two microscopical quantities: (i) the temperature parameter V , which contains the energy of inter-chain hydrogen bonding, (ii) $\varphi(m)$ which represents the relative statistical weight of the loop of length m . Both quantities can, in principle, be measured in experiments or be calculated by other independent methods. The function $\varphi(m)$ behaves differently for the small and large values of m (see Morozov et al., 2000 for details). It has been shown (Morozov et al., 2000) that the partition function for the Hamiltonian (4) of the linear DNA can be reduced to the Hamiltonian of the generalized polypeptide model (Hayryan et al., 1990; Hayryan et al., 1995)

$$-\beta H = J \sum_{i=1}^N \prod_{k=0}^{\Delta-1} \delta(\gamma_{i+k}, 1) \quad (10)$$

with the secular equation

$$\lambda^{\Delta-1}(\lambda - e^J)(\lambda - Q) = (e^J - 1)(Q - 1), \quad (11)$$

where Δ is the number of amino acid residues embraced by one intramolecular hydrogen bond for polypeptides, and $\Delta =$ the persistent length, for DNA.

In a similar way, it is possible to reduce the Hamiltonian of ccDNA also to the Hamiltonian of generalized polypeptide model. We are going to show this in the next section.

THE MODEL OF CLOSED CIRCULAR DNA

One can see easily that it is impossible to separate two chains of ccDNA completely, without breaking chemical bonds. Suppose at some part of the molecule some hydrogen bonds have been broken and a loop has formed. Then further growing of the loop or the formation of other loops becomes more and more difficult because there is no entropy gain to compensate the energetic losses. This means that the denaturing rate at each point of the molecule will depend on the conformation of the whole chain. Thus ccDNA is a system in which the state of repeated unit depends on the state of the whole molecule. Starting from this general observation and from the above described model of linear DNA, we construct the Hamiltonian for the ccDNA as follows.

We assume that in the Hamiltonian (4) the instantaneous value of the reduced energy of the hydrogen bonds $J = J(\eta)$ is a function of the fraction η of the broken hydrogen bonds in the molecule

$$\eta = 1 - \frac{1}{N} \sum_{k=1}^N \delta_1^{(k)}. \quad (12)$$

Note that η is not an averaged quantity. It characterizes the instantaneous degree of denaturing.

As a first step let us imagine $J(\eta)$ to be linear function of η

$$J(\eta) = J_0 + a + b\eta. \quad (13)$$

Here $J_0 = U/T$, U is the energy of hydrogen bond, a and b are some coefficients which depend on temperature.

Then the Hamiltonian (4) can be written as

$$-\beta H = (J_0 + a + b) \sum_{i=1}^N \delta_1^{(i)} - \frac{b}{N} \left[\sum_{i=1}^N \delta_1^{(i)} \right]^2 \quad (14)$$

The conformational partition function corresponding to the Hamiltonian (14) is

$$Z = \sum_{\{\gamma_k\}} \exp \left((J_0 + a + b) \sum_{k=1}^N \delta_1^{(k)} \right) \times \exp \left(\frac{b}{N} \left[i \sum_{k=1}^N \delta_1^{(k)} \right]^2 \right) \quad (15)$$

The imaginary unity in the argument of the second multiplier is introduced to ensure the positiveness of this term. This equation can be simplified by using the Hubbard-Stratanovich identities:

$$\exp \left(\frac{\varphi^2}{2g} \right) \sim \int_{-\infty}^{\infty} \left(-\frac{g}{2} x^2 + \varphi x \right) dx, \quad (16)$$

Hence

$$Z \propto \int_0^{\infty} dx \exp \left(-\frac{1}{4} \frac{N}{b} x^2 \right) \times \left[\sum_{\{\gamma\}} \exp(J_0 + a + b + ix) \sum_{k=1}^N \delta_1^{(i)} \right]. \quad (17)$$

In (??) the expression included in the square brackets is identical to the partition function Z_0 of a system with Hamiltonian (4) in which the reduced energy of the hydrogen bond

formation is replaced by

$$J = J_0 + a + b + ix. \quad (18)$$

In the thermodynamical limit

$$Z_0 \approx \lambda^N, \quad (19)$$

where λ is called *maximum characteristic Lyapunov exponent* (Crisanti et al., 1993) for Hamiltonian (4) and is a function of J described in (18).

At this point we can state that by redefinition of the hydrogen bond energy the model of ccDNA is reduced to the model of linear DNA which was itself reduced to the polypeptide model.

Then the partition function for the ccDNA is transformed to

$$Z \approx \int_0^\infty dx \exp \left(N \left(-\frac{1}{4} \frac{x^2}{b} + \ln \lambda \right) \right). \quad (20)$$

For large N the integral can be evaluated using the saddle point method

$$Z \approx \exp \left(N \left(-\frac{1}{4} \frac{x_0^2}{b} + \ln \lambda_0 \right) \right), \quad (21)$$

where λ_0 is the value of Lyapunov exponent at the saddle point and is a function of argument $(J_0 + a + b + ix_0)$, x_0 is obtained from the condition that the element of integration takes its maximum at the saddle point.

For λ we have from Hamiltonian (4)

$$\frac{\partial \ln \lambda}{\partial J} = \frac{1}{NZ} \sum_{\{\gamma_i\}} \sum_i \delta_1^{(i)} \exp \left(J \sum_i \delta_1^{(i)} \right) \equiv \theta, \quad (22)$$

where θ is the degree of helicity for the open DNA or the average fraction of the repeated units in the helical conformation.

The free energy per repeated unit is

$$f = \ln \lambda(J) + b\theta^2, \quad (23)$$

where J from (18) is reduced to

$$J = J_0 + a - b + 2b(1 - \theta). \quad (24)$$

Thus we see that the helicity degree θ for the linear chain emerges in the partition function of circular molecule as a parameter.

MELTING CURVES FOR CLOSED CIRCULAR DNA AND LINEAR DNA

From the partition function, we can evaluate the helicity degree of ccDNA

$$\Theta = \frac{1}{N} \frac{\partial \ln Z}{\partial J_0} = \frac{\partial f}{\partial J_0}. \quad (25)$$

Straightforward calculations lead to

$$\Theta = \theta \cdot \left[1 - 2b \frac{\partial \theta}{\partial J_0} \right] + [2b\theta] \frac{\partial \theta}{\partial J_0} = \theta. \quad (26)$$

Though the equations for the free energy are different for ccDNA and linear DNA, the dependence of helicity degree on the respective reduced energy of hydrogen bonds of each model is the same. This means that the degree of helicity in ccDNA can be obtained from that of linear chain by redefinition of reduced energy of hydrogen bonding by the formula (24).

From (24) one can easily obtain the relation between the temperatures corresponding to the equal values of helicity degree for linear and ccDNA.

$$T_C = T_L [1 + (\alpha - \beta) + 2\beta(1 - \theta)]. \quad (27)$$

Here T_C and T_L are temperatures of ccDNA and linear DNA, respectively, $\alpha = a/J_0$, $\beta = b/J_0$. Eq. (27) allows to calculate the denaturing curve for ccDNA from the melting curve of corresponding linear molecule (Fig.3).

In (Gagua et al., 1981) the experimental differential denaturing curve of the mixture of linear and ccDNA in the solvent has been presented, which shows equality of melting temperatures of GC and AT pairs. One can observe that the transition in the linear molecule occurs within a much more smaller temperature interval ($\sim 1^\circ$) than in ccDNA ($\sim 20^\circ$). Besides, the melting process in ccDNA begins earlier and completes at higher temperature.

Let us try to explain this fact in the framework of the present model. For the sake of simplicity suppose that the melting of linear DNA occurs as a pure phase transition (Fig. 4a) and let $\alpha - \beta < 0$, $\beta > 0$. Then the denaturing curve of ccDNA from Eq. (27) will be represented by a linear function of temperature.

$$1 - \theta = \frac{T}{T_M} \cdot \frac{1}{2\beta} + \frac{\beta - \alpha - 1}{2\beta}, \quad (28)$$

where T_M is the transition temperature. This equation is true in the temperature interval from $T_1 = T_M(1 - (\beta - \alpha))$ to $T_2 = T_M(1 + \alpha + \beta)$. As shown in Fig. 4b, we have

$$\frac{\partial(1 - \theta)}{\partial T} = \frac{1}{2\beta T_M}, \quad (29)$$

for $T_1 < T < T_2$. This means that while the linear DNA undergoes a sharp transition at certain temperature T_M , the transition in ccDNA has a finite interval, given by Eq. (29). Thus, within the present model it is possible to describe qualitatively considerable widening of the transition interval of ccDNA as compared to the linear molecule as well as shifting of the left point of the transition interval toward low temperatures.

Another experimental fact is that the differential melting curve of linear DNA of higher organisms has very rugged form while the melting curve of ccDNA is relatively smooth. This result can be explained as follows. It is widely believed that each peak at the DMC corresponds to the melting of particular region of DNA. Thus, each of these regions melts as mini-DNA. Consequently, every peak at the DMC corresponds to the S-like region of the melting curve, containing inflection point. The temperature transformation, described by Eq.(??), makes each of these regions more flat in analogy with the whole melting curve. It makes the DMC much more smooth. Our calculations (in agreement with our previous results obtained in the particular case) show that the curves are smooth, melting begins earlier and the transition interval is very large. One can see that the calculated curves possess all three features of ccDNA: the curves are smooth, melting begins earlier and the transition interval is very large.

CONCLUSION

We have constructed the model for the ccDNA using the earlier developed model for the linear DNA. The connection between two models is defined by the universal behavior of

the order parameter (helicity degree) vs the reduced energy of formation of hydrogen bonds between complementary pairs. The parameters α , β in the expression of $J(\eta)$ are closely related to the topology and energetics of superhelic structure. In further work it is necessary to try to establish these relations explicitly.

It would be interesting also to include higher power terms in Eq. (13) and evaluate the corresponding transformation formula for the melting temperatures.

$$T_C = T_L(1 + (\alpha - \beta) + 2(\beta - \gamma)(1 - \theta) + 3(\gamma - \delta)(1 - \theta)^2 + 4(\delta - \epsilon)(1 - \theta)^3 \dots) \quad (30)$$

Note that the comparison of the results with the experimental data is done only qualitatively. We have just predicted the widening of the melting interval, smoothening of the melting curve and disappearing of some sequence dependent details.

To compare the theory with the experimental data quantitatively, it is necessary to carry out experiments on melting of the ccDNA with certain superhelicity (with certain α , β , γ ...) and of the linear chain under the identical conditions.

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Figure Caption

FIGURE 1 Schematic diagram of closed circular DNA.

FIGURE 2 Schematic diagram for construction of Hamiltonian for linear DNA.

FIGURE 3 Transformation of the melting curve of linear DNA (left) into the melting curve of ccDNA (right). The horizontal axis corresponds to the temperature ($T^{\circ}K$). The vertical axis shows the fraction of the open bonds (dimensionless).

FIGURE 4 (a) The scheme of transformation of melting curve for infinitely sharp helix-coil transition. Along the horizontal axis is the temperature ($T^{\circ}K$). The vertical axis shows the fraction of the open bonds (dimensionless). (b) Transformation of the differential melting curve for infinitely sharp helix-coil transition. The vertical axis shows the derivative of the fraction of the open bonds, in units $1/T$.



Fig.1 . Morozov, *et al.*

FIG. 1:



Fig.2. Morozov et al

FIG. 2:

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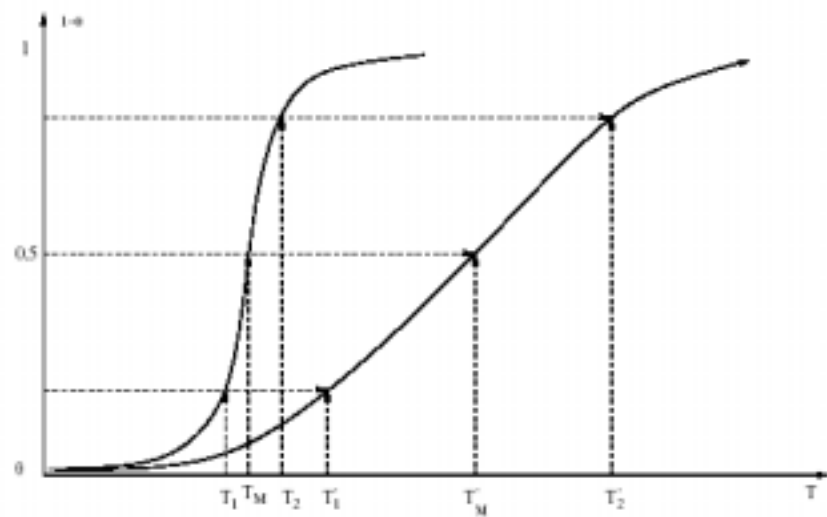


Fig.3. Morozov, et al.

FIG. 3:

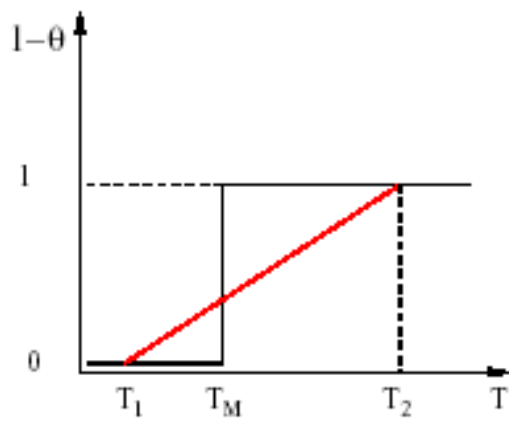


Fig. 4a. Morozov, et al.

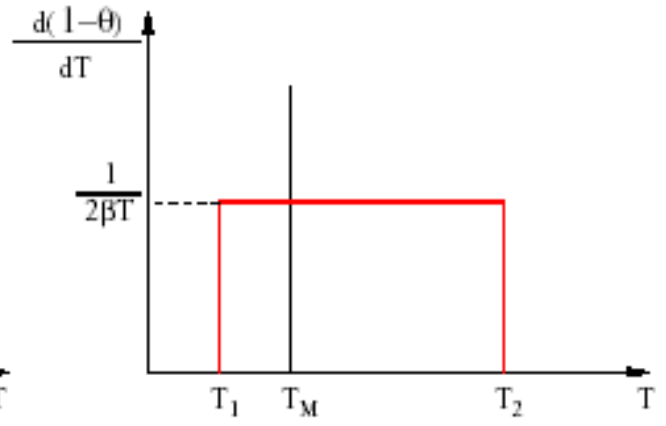


Fig. 4b. Morozov, et al.

FIG. 4: